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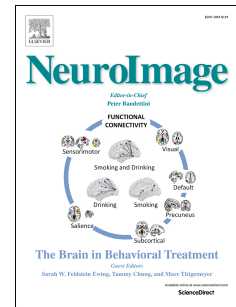
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# Accepted Manuscript

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## Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis

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**Abstract**

Hippocampal volume increase in response to aerobic exercise has been consistently observed in animal models. However, the evidence from human studies is equivocal. We undertook a systematic review to identify all controlled trials examining the effect of aerobic exercise on the hippocampal volumes in humans, and applied meta-analytic techniques to determine if aerobic exercise resulted in volumetric increases. We also sought to establish how volume changes differed in relation to unilateral measures of left/right hippocampal volume, and across the lifespan. A systematic search identified 4398 articles, of which 14 were eligible for inclusion in the primary analysis. A random-effects meta-analysis showed no significant effect of aerobic exercise on total hippocampal volume across the 737 participants. However, aerobic exercise had significant positive effects on left hippocampal volume in comparison to control conditions. Post-hoc analyses indicated effects were driven through exercise preventing the volumetric decreases which occur over time. These results provide meta-analytic evidence for exercise-induced volumetric retention in the left hippocampus. Aerobic exercise interventions may be useful for preventing age-related hippocampal deterioration and maintaining neuronal health.

**Keywords:** physical activity; plasticity; neurogenesis; neurodegeneration; hippocampus; resistance

## 1. Introduction

The hippocampus is one of the major brain sites of neuroplasticity, and has been identified as a brain region sensitive to the effects of physical activity, and in particular aerobic exercise interventions (Cotman et al., 2007). The impact of aerobic exercise on hippocampal size and function has been extensively studied in rodents (Van Praag et al., 2005). These animal studies have shown that voluntary exercise is associated with hippocampal neurogenesis (Van Praag, 2008) and prevents age-related decline in cell-proliferation in this brain structure. Changes in hippocampal structure may be mediated by trophic factors, such as insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) (Ferris et al., 2007; Vaynman et al., 2004). Angiogenesis may also contribute, with evidence that dentate gyrus cerebral blood volume (CBV) is increased after exercise in rodents (Swain et al., 2003; Van Praag et al., 2005). In addition, dentate gyrus CBV was significantly associated with increased oxygen uptake ( $VO_2$ ) following aerobic exercise in healthy human volunteers ( $r = .66$ ,  $p < 0.05$ ,) (Pereira et al., 2007). Such changes have also been linked to cognitive benefits in both animal and human studies (Adlard et al., 2005; Kimhy et al., 2015).

Whilst there is clear evidence in animal studies that exercise training is associated with increased hippocampal neurogenesis, the evidence from human studies is equivocal. Along with a recent meta-analysis showing that physical activity is correlated with greater white matter volume (Sexton et al., 2016), there are also several studies reporting cross-sectional relationships between physical activity

levels and hippocampal volumes (Erickson et al., 2010). However, determining causality from such correlational analyses is not possible.

Some randomized controlled trials (RCTs) have reported exercise-induced increases in hippocampal volumes. For instance, Pajonk et al. (2010a) and Erickson et al. (2011a) demonstrated that exercise increased hippocampal volumes among people with schizophrenia and older adults respectively. A previous review of exercise-induced changes in brain regions implicated in the default mode network also presented some preliminary evidence that exercise increased right hippocampal volume (Li et al., 2016). However, these findings were limited to four studies, with a combined total of 132 participants receiving exercise interventions. Since this review, a number of large controlled studies have been published (e.g. Jonasson et al., 2016; Maas et al., 2015; Lin et al., 2015; Rosano et al., 2016; Malchow et al., Thomas et al., 2016) – but again with equivocal findings.

We conducted a systematic review and meta-analysis to determine the impact of aerobic exercise interventions on hippocampal volumes in human subjects. We included controlled studies conducted in human subjects, regardless of age or clinical status. We also conducted a range of subgroup analyses to explore effects of exercise in unilateral measures of left/right hippocampal volume, and establish effects on the hippocampus in clinical and non-clinical populations. Additionally, we employed meta-regression techniques to examine how exercise effects differed with age.

## **2. Methods**

### **2.1. Search Procedure**

This systematic review was prospectively registered with the PROSPERO database (#CRD42014009686) and was conducted in accordance with the MOOSE guidelines (Stroup et al., 2000) and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (Moher et al., 2009). Two independent authors (SR, JF) searched Medline, PsycARTICLES, AMED, Embase and CINAHL from database inception to August 14<sup>th</sup> 2017 for controlled intervention studies. Key words used were “exercise” AND “hippocampus” OR “hippocampal volume” in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles. After the removal of duplicates, both reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (BS) was available for mediation throughout this process, however this was not required due to consistent agreement between reviewers.

### **2.2. Participants**

Inclusion in this review was restricted to studies of adults aged at least 18 years. Studies were included regardless of clinical diagnosis at the time of assessment. All populations were used in main analysis, with subgroup analyses used to explore how the effects of exercise on hippocampal volume differ with respect to clinical status.

### **2.3. Interventions**

Exercise interventions were defined as physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of physical fitness or health as an objective (Caspersen et al. 1985). We restricted this review to aerobic exercise interventions only and excluded other physical activity interventions such as resistance training, as these alternative methods of exercise have different neurological actions to aerobic training (Cassilhas et al., 2012).

### **2.4. Control conditions**

Studies were considered eligible if they examined the effects of a structured, aerobic exercise intervention on hippocampal volumes in comparison to an inactive control condition, or a time-and-attention matched comparator of minimal activity (such as stretching or balance training), of a similar duration. Studies which compared two forms of aerobic exercise, without a non-aerobic exercise comparator, were unable to be included.

### **2.5. Outcome measures**

The primary outcome measure was absolute hippocampal volume assessed via structural magnetic resonance imaging (MRI) and estimated using either manual tracing or automated methods. We included both bilateral and unilateral (i.e. left and right) measures of the hippocampus. The method of assessment was recorded. When more than three studies were identified recruiting participants with similar diagnoses (e.g. mental disorders), subgroup analyses were conducted.



## **2.6. Exclusion criteria**

We excluded studies with: (a) insufficient data for extraction of primary outcome data; (b) restriction to children and/or adolescents, (c) animal studies and (d) non-exercise interventions. In the case of multiple publications from the same study, only the most relevant paper or article was included. There were no language or time restrictions placed upon identified articles.

## **2.7. Quality assessment**

The quality of included studies was assessed using the Cochrane's Collaboration risk of bias tool (Higgins, 2011). This tool was applied to rank each study for 'Low', 'High' or 'Unclear' risk of bias for six aspects of trial design that could introduce different sources of bias (sequence generation, allocation sequence concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other sources).

## **2.9. Statistical Analyses**

Random-effects meta-analyses were conducted using Comprehensive Meta-Analysis software (Version 2). Intervention effect sizes (differences between intervention and control groups) for the primary outcome measure (hippocampal volume) at post-treatment, were calculated using Hedges'  $g$  statistic, along with 95% confidence intervals (CIs) around the estimated effect-size. Intervention effect sizes were also calculated to determine effects of exercise on hippocampal volume in (i) studies using automated vs. manual segmentation methods, and (ii) unilateral measures of left and right hippocampal volume. No study reported a pre and post-test

correlation, therefore we assumed a conservative correlation of 0.7 for the primary outcome. Effect sizes were categorized as small (0.2), medium (0.5), or large (0.8 or greater (Cohen, 1988). Statistical heterogeneity was quantified using the  $I^2$  statistic:  $I^2$  of more than 75% is considered to indicate considerable heterogeneity,  $I^2$  of 50%–75% is considered to indicate substantial heterogeneity, and an  $I^2$  of less than 40% is considered to indicate limited heterogeneity. Publication bias was tested using the Egger's regression method and Begg & Mazumdar test, with a p-value <0.05 suggesting the presence of bias (Begg and Mazumdar, 1994; Egger et al., 1997). Where significant bias was detected, a Duval and Tweedie (2000) trim-and-fill analysis was applied. In addition, a funnel plot was created, in which the study-specific effect estimates are displayed in relation to the standard error in order to assess the potential presence of publication bias. Subgroup analyses were conducted to examine the effects of exercise on bilateral and unilateral hippocampal volume for any population studied by >2 trials. Furthermore, meta-regression analyses were used to explore the relationship between mean sample age (years) and intervention effect size.

## Results

### 3.1. Search results and flow of trials through the review

A total of 4398 records were identified, reduced to 2260 after duplicates were removed. After screening and the application of the eligibility criteria, 14 eligible studies were identified and included in the primary meta-analysis (hippocampal volume). Figure 1 presents the flow of studies through the review.

*Figure 1 here*

### 3.2. Characteristics of Included Trials

Table 1 summarizes the characteristics of included trials, including participant characteristics, summary of the intervention, and control group protocol. Fourteen trials were included, with eligible outcome data from 737 participants. Participants mean age in the included trials ranged from 24 to 76 years (median = 66 years). Four studies recruited participants with a DSM diagnosis of schizophrenia or other psychotic disorders (Lin et al., 2015; Malchow et al., 2016; Pajonk et al., 2010a; Scheewe et al., 2013a), six recruited healthy older adults (Burzynska et al., 2017; Erickson et al., 2011a; Kleemeyer et al., 2016; Maass et al., 2015; Niemann et al., 2014b; Rosano et al., 2016), whilst individual studies examined the effects of exercise of hippocampal volumes in people with depression (Krogh et al., 2014a), mild cognitive impairment (Brinke et al., 2014), probable Alzheimer's disease (Morris et al., 2017), and healthy young-middle aged adults (Thomas et al., 2016). Study participants were recruited from the general community (Burzynska et al., 2017; Erickson et al., 2011a; Jonasson et al., 2016; Kleemeyer et al., 2016; Krogh et al.,

2014b; Maass et al., 2015; Niemann et al., 2014b; Rosano et al., 2016; Thomas et al., 2016), university medical clinics (Brinke et al., 2014), community or outpatient treatment or referred from clinical settings (Lin et al., 2015; Malchow et al., 2015; Morris et al., 2017; Pajonk et al., 2010a; Scheewe et al., 2013b).

Risk of bias assessments found that studies varied in their quality and only three studies met the Cochrane standard for Low Risk of bias on all criteria (Burzynska et al., 2017; Krogh et al., 2014; Lin et al., 2015). The results of bias assessments for each study are displayed in Supplement 1.

### **3.3. Interventions**

Four of the studies utilised a stationary cycling intervention (Thomas et al., 2016, Krogh et al., 2016; Pajonk et al., 2010; Malchow et al., 2015), five studies investigated walking-based interventions (Burzynska et al., 2017; Niemann et al., 2014; Erickson et al., 2011; Brinke et al., 2015; Rosano et al., 2016), four combined multiple modalities of aerobic exercise (Lin et al., 2015; Jonasson et al., 2016; Morris et al., 2017; Scheewe et al., 2013;), and one used treadmill running (Maas et al., 2015). The length of the interventions ranged from three to 24 months with a range of 2-5 sessions per week (see Table 1). All studies used supervised exercise sessions.

*Table 1 here*

### **3.4. The effect of aerobic exercise on hippocampal volume**

Results from all meta-analyses are presented in Table 2. Eligible outcome data was available from 14 studies investigating the effect of aerobic exercise on hippocampal volume. Pooled effects across 737 participants (387 in exercise interventions and

350 controls) showed a non-significant effect of exercise on total hippocampal volume (Hedges  $g = 0.120$ , 95% CI:  $-0.02$  to  $0.26$ ,  $p=0.082$ , Figure 2). There was some no evidence of heterogeneity ( $Q=14.05$ ,  $p=0.371$ ,  $I^2=7.45\%$ ) and indication of publication bias (Kendall tau= $0.451$ ,  $p=0.014$ , Eggers regression = $0.771$ ,  $p=0.13$ ). The trim-and-fill analysis identified one outlier studies introducing publication bias, further reducing the non-significant effect (Adjusted  $g=0.104$ , 95% CI= $-0.05$  to  $0.26$ ). Sensitivity analyses confirmed that null effects of exercise on hippocampal volume were found from studies using automated segmentation ( $N=7$ ,  $n=407$ ,  $g=0.167$ , 95% C.I.=  $-0.01$  to  $0.34$ ,  $p=0.06$ ) and manual segmentation ( $N=6$ ,  $n=254$ ,  $g=0.118$ , 95% C.I.=  $-0.13$  to  $0.36$ ,  $p=0.34$ ), with no significant differences between these two methods ( $Q=0.113$ ,  $p=0.74$ ).

*Figure 2 here*

Meta-analyses were also performed for the nine studies (total  $n=501$ ) that reported changes in left and right hippocampal volumes separately (Figure 3). This showed no significant effect of exercise on right hippocampal volumes ( $g=0.164$ , 95% CI=  $-0.01$  to  $0.34$ ,  $p=0.065$ ). However, aerobic exercise had significant positive effects on left hippocampal volume in comparison to control conditions ( $g=0.265$ , 95% CI=  $0.09$  to  $0.44$ ,  $p=0.003$ ) and there was no indication of heterogeneity ( $I^2=0\%$ ) or publication bias influencing these results (Kendall tau= $0.19$ ,  $p=0.23$ , Eggers regression= $0.23$ ,  $p=0.40$ ). In order to explore if the positive effects of exercise were due to increasing hippocampal volume, rather than attenuating volume loss in comparison to control conditions) post-hoc analyses were performed to pool the mean changes in left hippocampal volume reported in the exercise conditions. Raw change data was

available for 8 studies (total  $n=256$ ) no significant increase in left hippocampal volume following the exercise interventions ( $g=0.049$ , 95% C.I.= -0.06 to 0.16,  $p=0.384$ ), thus indicating the positive effects observed in the primary analysis are due to exercise attenuating age-related neurodegeneration (rather than exercise significantly increasing hippocampal volume).

*Figure 3 here*

### **3.5. The effect of aerobic exercise on hippocampal volume in healthy older adults**

Data was pooled from six studies to determine the effect of aerobic exercise on hippocampal volume in healthy older adults ( $n=390$ ). Aerobic exercise did not significantly increase total hippocampal volume compared to control conditions ( $g=0.146$ , 95% CI: -0.011 to 0.303,  $p=0.07$ ). Five studies (total  $n=332$ ) reported effects of exercise on left/right hippocampus separately. There was a statistically significant positive effect of exercise in left hippocampal volume in healthy older adults ( $g=0.355$ , 95% CI= 0.14 to 0.57,  $p=0.001$ ), with no indication of heterogeneity or publication bias influencing these results. There was also a significant effect of exercise on right hippocampal volume in healthy older adults ( $g=0.237$ , 95% CI=-0.02 to 0.45,  $p=0.032$ ), again with no indication of heterogeneity or publication bias. Post-hoc analyses examining raw volumetric changes in exercise conditions alone found that exercise in older adults did not significantly increase volume in the left ( $N=4$ ,  $n=168$ ,  $g=0.04$ ,  $p=0.70$ ) or right hippocampus ( $g=0.034$ ,  $p=0.71$ ), again indicating that positive effects observed from exercise are due to slowing down or preventing the volume loss occurring over time among the older adults in control conditions.

### **3.6. The effect of aerobic exercise on hippocampal volume in patients with psychotic disorders**

Four studies examined the effect of aerobic exercise on hippocampal volume in people with schizophrenia or first episode psychosis ( $n=107$ ). Aerobic exercise did not significantly increase total hippocampal volume compared to control conditions ( $g= 0.149$ , 95% CI:  $-0.31$  to  $0.60$ ,  $p=0.53$ , Table 2). Among the two studies which reported effects on left/right hippocampus separately, there was no evidence of effects in either region (both  $p>0.1$ ). There was also no evidence of heterogeneity or publication bias influencing these results.

### **3.7. The effect of aerobic exercise on hippocampal volume in other populations**

Data in other populations was insufficient for pooled meta-analyses, and so results from individual trials are summarised below. Individual trials which examined effects of aerobic exercise in patients with depression (Krogh et al., 2014), mild cognitive impairment (Brinke et al., 2014) and probable Alzheimer's disease (Morris et al., 2017) all found no significant effects on total or left/right hippocampal volumes. One study examining the effects of exercise in young-to-middle-aged adults found no change in total hippocampal volume but did find a significant increase in anterior hippocampal volume following 6 weeks of aerobic exercise (Thomas et al., 2016).

### **3.8. Effects of exercise in relation to participant age**

Meta-regression analyses were performed to examine the relationship between mean sample age and effects of exercise on hippocampal volume. No statistically

significant associations of effects of exercise with sample age were found for total, right or left hippocampal volume (all  $p > 0.05$ ).

#### 4. Discussion

This meta-analysis examined the effects of exercise on hippocampal volumes in clinical and non-clinical populations. Fourteen controlled trials comparing aerobic exercise with various control conditions were eligible for inclusion, with a total of 737 participants. Random effects meta-analyses found that aerobic exercise had no effect on total hippocampal volumes (Figure 2), with no statistical heterogeneity between studies. This finding is consistent with that of a previous review which also found no effect of aerobic exercise on total hippocampal volume (Li et al., 2016), although in an analysis that included fewer studies of a smaller number of participants (Five studies, 184 participants).

The current meta-analysis revealed a significant effect of aerobic exercise on left hippocampal volumes ( $g = 0.265$ , 95% CI = 0.1 to 0.44,  $p = 0.003$ ). Interestingly, Li et al., (2016) reported significant effects of exercise in the right hippocampus, but no statistically significant changes in the left hippocampus. The current analyses included more than twice as many controlled trials, comprising a total of nine studies (including five newer studies which were not available for inclusion in the earlier review). Moreover, the earlier meta-analysis examined post-intervention differences in hippocampal volume and therefore could not account for baseline volumes of the hippocampus or the mean change from pre to post test. Given that some of the controlled trials were not randomized and included relatively small numbers of participants, relying solely on posttest changes does not take into



account group differences at baseline, which may have impacted the findings.

Furthermore, there was no evidence of heterogeneity or publication bias influencing our results. Nonetheless, the findings should be interpreted with some caution due to the fact that all but two studies had potentially moderate/high risk of bias.

The same observation of exercise having significantly positive effects on left hippocampal volume was also observed for the subgroup of studies conducted in healthy older adults ( $g=0.36$ ,  $p=0.001$ ). The demonstrated potential for exercise to positively affect hippocampal volume in healthy older adults has important implications, since neuronal mass decreases with increasing age in this area in almost all people during healthy ageing (Raz et al., 2005), and is associated with cognitive decline (Mosconi et al., 2008). In the ageing population, the potential benefits of any intervention which attenuates cognitive decline would have a substantial positive impact on public health. Indeed, our post-hoc analyses indicated that the positive effects of exercise on hippocampal volume were observed as a result of exercise promoting retention of hippocampal volume (while volume loss occurred in control conditions), rather than actually increasing neuronal mass per-se. However, given the limited number of studies in this analysis, caution is required when interpreting this result.

No significant effects from exercise were observed in people with schizophrenia, although only two studies could be included in the subgroup analysis examining left hippocampal volume change from exercise in this population (total  $n=69$ ). Similarly, we did not find any significant effects from exercise on left, right or total hippocampal volume in people with depression (Krogh et al., 2014), mild cognitive

impairment (Brinke et al., 2014) or probable Alzheimer's disease (Morris et al., 2017). However, meta-analyses were not possible for these samples, given there was only data from single studies for each patient group. Considering also that all of these studies had small sample sizes, it is equally likely that the non-significant effects observed in these clinical populations are due to underpowered studies. Thus, the possible benefits of exercise for hippocampal volume in schizophrenia, depression or cognitive impairment cannot yet be ruled out on the basis of our null findings.

The neurochemical mechanisms through which exercise promotes retention of hippocampal volume in aging humans has not been fully established. However, a comprehensive narrative review examining the neurological effects of exercise across the lifespan (Voss et al., 2011) found evidence from animal models supporting the theory that aerobic exercise acts by preventing the usual decrease in neurogenesis associated with aging, thus resulting in greater retention of neural matter – particularly in the hippocampus. Whereas angiogenesis (i.e. increase in brain vasculature) may also be induced by aerobic exercise, this is not observed in animal models using older rodents, and increases in cognitive performance occur independently of vascular changes (Van Praag et al., 2005). Voss et al., (2011), concluded that the primary candidate for stimulating neurogenesis in relation to exercise is BDNF. The findings of the current review are consistent with this suggestion, as BDNF is found in high concentrations within the hippocampus (Murer et al., 2001) and recent meta-analytic evidence has demonstrated this is upregulated by regular exercise in humans (Szuhany et al., 2015).

Another factor that may contribute to the more consistent effects of exercise on hippocampal volumes observed among older adults is the likelihood that there may have been greater consistency of non-intervention specific physical activity among older adults. As one of the most plastic regions of brain, the hippocampus is more likely to reflect the impact of a wide range of non-specific behavioral effects that are more difficult to constrain in human subjects than in laboratory animals. This would in turn reduce the capacity to determine exercise-specific hippocampal volume changes in human subjects.

The effects of exercise on hippocampal volume in humans have also been linked with improvements cardiorespiratory fitness. Cross-sectional studies have previously reported a link between fitness and brain volumes (Erickson et al., 2014), and several of the RCTs also observed a positive association of volumetric changes in the hippocampus with exercise-induced fitness improvement (Erickson et al., 2011b; Kleemeyer et al., 2016; Pajonk et al., 2010b). Again, the mechanistic link between these two variables is unclear. Nonetheless, these findings hold important implications from an implementation perspective, as while it may be difficult to develop exercise programs specifically for improving brain volume, focusing on fitness improvement appears to be one method for designing exercise interventions to confer neurobiological benefits. Indeed, previous research has shown that increases in cardiorespiratory fitness are also positively associated with the improvements in cognitive performance which occur from exercise, in both clinical and non-clinical populations (Firth et al., 2016; Hötting and Röder, 2013). Considering this alongside the broader benefits for metabolic risk (Kodama et al.,

2009), physical capacities (Lord et al., 2003), and mental health (such as reducing depression) (Schuch et al., 2016; Sui et al., 2009), prescribing aerobic exercise with an emphasis on cardiorespiratory fitness enhancement appears to be a suitable intervention for promoting healthy aging, in order to maintain both physical and neurological functioning into old age.

There are limitations to this review, which are largely reflected by limitations in the primary studies. One limitation of this review that we examined changes only in hippocampal volume, without analyzing other brain regions. Although the hippocampus has long been recognized as a particularly sensitive region for detecting exercise-induced alterations in both animal and human studies (Hillman et al., 2008; Molteni et al., 2002), other areas are also important to examine for future research (see Table 1). For instance, Malchow et al. (2015) showed that aerobic exercise significantly increased brain volume in various areas of the temporal gyri in people with schizophrenia, independently of hippocampal volume change. Additionally, there is growing evidence that exercise may alter structure and connectivity in white matter regions (Riggs et al., 2017; Voss et al., 2013) and the basal ganglia - changes which are further related to the cognitive and functional improvements which occur from aerobic exercise (Niemann et al., 2014a).

Additionally, although we found an overall effect of aerobic exercise on left hippocampal volume, the intensity, frequency and length of exercise programs differed considerably across the studies, and was not reported in sufficient detail to perform comparative subgroup meta-analyses; thus making it difficult to determine which intervention factors are most important for influencing hippocampal volume.

Perhaps most importantly, the exercise interventions were all relatively short (mostly <12 months) and longer, adequately powered RCTs are required to consider if exercise can influence hippocampal volume over the longer term. Future research which compares different exercise modalities, along with varying the frequency and intensity of aerobic training, could provide new insights into optimal program design. However, it is important that a 'fair' comparator is given when comparing exercise to a control condition, since active controls in other studies have demonstrated considerable improvements in primary outcomes (Stubbs et al., 2016).

Furthermore, the neurobiological benefits of non-traditional approaches towards aerobic fitness improvement should also be established. For instance, 'high intensity interval training' (HITT) has recently been shown to produce similar cardiovascular benefits to long-duration endurance training in short periods of times (Wisløff et al., 2009), although the effects on brain health have yet to be established.

One further consideration is that evidence is currently lacking with regards to a direct link between exercise-induced increases in brain volume and actual cognitive benefits in terms of task performance. Assuming that greater brain volume is directly associated with better neural functioning and thus cognitive task performance is reductive, and does not follow from the available evidence (Eyler et al., 2011).

Indeed, one of the studies in this review even found a negative relationship; with exercise-induced increases in the left hippocampus significantly associated with worse cognitive performance after a 6-month intervention (Ten Brinke et al., 2015).

Thus, although exercise significantly increased some areas of hippocampal volume and cognition in humans, it cannot be concluded that structural increases are

causative or necessary for performance increases (Hillman et al., 2008). This is also true for white matter regional increases, as although cardiorespiratory fitness is linked to both improved white matter integrity and cognitive performance, there is no independent link between these variables (Voss et al., 2013).

In conclusion, this meta-analysis found no effects of exercise on total hippocampal volume, but did find that exercise interventions retained left hippocampal volume significantly more than control conditions. As these positive effects were also observed among the subgroup of studies of healthy older adults, the findings hold promising implications for using exercise to attenuate age-related neurological decline. Currently, the overall quality of the evidence is compromised by the fact that 10 of the 12 studies included some risk of bias, therefore more high-quality RCTs are now required. In addition to RCTs, a prospective meta-analysis examining how changes in physical activity and fitness predict hippocampal retention/deterioration across the lifespan would provide novel insights into longer-term neural effects of exercise, while also reducing the impact of methodological heterogeneity often found across exercise RCTs. Further research is also required to determine effects in younger people (Riggs et al., 2017), and establish the neurobiological mechanisms through which exercise exerts these effects, in order to design optimal exercise programs for producing neurocognitive enhancements. However, the functional relevance of structural improvements has also yet to be ascertained. Nonetheless, the link between cardiorespiratory fitness with both structural and performance increases indicates this as a suitable target for aerobic training programs to improve brain health.

## Conflict of Interests

All authors declare no conflict of interests

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## Figure Legends

Figure 1. PRISMA flow diagram of systematic search and study selection.

Figure 2. Forest-plot showing effects of exercise on total hippocampal volume across all studies. Box size represents study weighting. Diamond represents overall effect size and 95% confidence intervals.

Figure 3. Meta-analyses of unilateral measures across 9 studies with, showing effects of exercise on left and right hippocampal volumes separately. Box size represents

study weighting. Diamond represents overall effect size and 95% confidence intervals.

### Supplementary Information

Supplement 1. Risk of bias summaries for included studies.

Supplement 2. Funnel-plot of publication bias.

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Trial	Included subjects	Age mean (SD)		% Male	Participants	Control condition	Intervention details	Segmentation method	Effects in other brain regions
		Exp	Ctrl						
Brinke et al (2015)	21	76.07	75.46	0	Mild cognitive impairment	Balance and tone training	Six-month outdoor walking program (60 mins, 2x/wk for 6 months) at 40% of HR reserve progressing to 70-80% HR reserve.	Automated ('FIRST' tool)	N/R
Burzynska et al. (2017)	124	65.0	66.7	31	Older adults	Stretching and toning	Six-month outdoor walking program (40mins, 3x/wk) at 50-60% of max HR progressing to 60-75% of max HR.	Automated (in 'Freesurfer')	White matter decreased equally in walking and stretching conditions.
Erickson et al (2011)	120	67.6	65.6	33	Older adults	Stretching and toning	12 month walking program (40mins, 3x/wk) at 50-60% HR reserve progressing to 60-75% HR reserve	Automated ('FMRIB' tool)	Non-significant increase in thalamus volume [ $F(2,114) = 0.24$ ; $P < 0.80$ ]. Exercise slightly attenuated caudate nucleus volume loss, although this was not significant.
Jonasson et al (2016)	58	68.4	69.0	48	Older adults	Stretching and toning	6 month jogging and cycling program (30-60mins, 3x/wk) at 40-80% of estimated maximal HR	Manual (in 'Freesurfer')	No changes in dorsolateral/ventrolateral prefrontal cortex, or anterior cingulate cortex.
Krogh et al (2014)	79	38.9	43.8	33	Major depressive disorder	Stretching	3 months stationary cycling (45mins, x3/wk) at approximately 80% maximum HR.	Manual (in MATLAB's 'RIP')	N/R
Lin et al (2015)	30	23.8	25.3	0	First episode psychosis	Usual treatment	3 months of aerobic training on treadmill and bicycle (45–60 min, x3/wk) at 50%–60% VO2 max.	Automated (with 'FSL FAST').	N/R

Maas et al (2015)	32	68.4	68.4	45	Older adults	Stretching and muscle relaxation	3 months of treadmill running (30min, x3/wk) at 65%-85% HR reserve.	Manual (with 'MRICron')	Indication of exercise increasing total gray matter volume
Malchow et al (2015)	39	37.4	35.3	68	Schizophrenia	Table-top football	3 months stationary cycling (30mins, 3x/wk) at individualised intensity according to blood lactate concentration of approximately 2 mmol/L	Manual (in 'Freesurfer')	Exercise significantly increased the left superior, middle and inferior anterior temporal gyri.
Morris et al. (2017)	68	71.4	74.4	49	Probable Alzheimer's disease	Stretching and toning	24 weeks of supervised aerobic exercise sessions aiming to achieve 150 mins per week at 60-75% HR reserve.	N/S (done using Freesurfer)	No effects of exercise on total gray matter volume
Niemann et al (2014)	30	68.2	68.8	35	Older adults	Stretching and relaxation	12 months Nordic walking (45 mins, 3x/wk) at individualised intensity above aerobic threshold, but below anaerobic threshold (~60% VO <sub>2</sub> peak)	Manual (using 'Analyze 10.0')	N/R
Pajonk et al (2010)	16	32.9	37.4	100	Schizophrenia	Table-top football	3 months stationary cycling (30 mins, 3x/wk) at heart rate ( $\pm 10$ beats/min) corresponding to a blood lactate concentration of about 1.5 to 2 mmol/L (14-18 mg/dL).	Manual (in 'Analyze' and 'SPM99')	N/R
Rosano et al (2016)	26	73.8	76.4	30	Older adults	Health education	24 months of moderate-intensity walking (40 mins, x2/wk) with other physical activities.	Automated (in 'FIRST')	Hippocampal subregions: Non-significant increase in left cornu ammonis from exercise, and no change



in dentate gyrus.

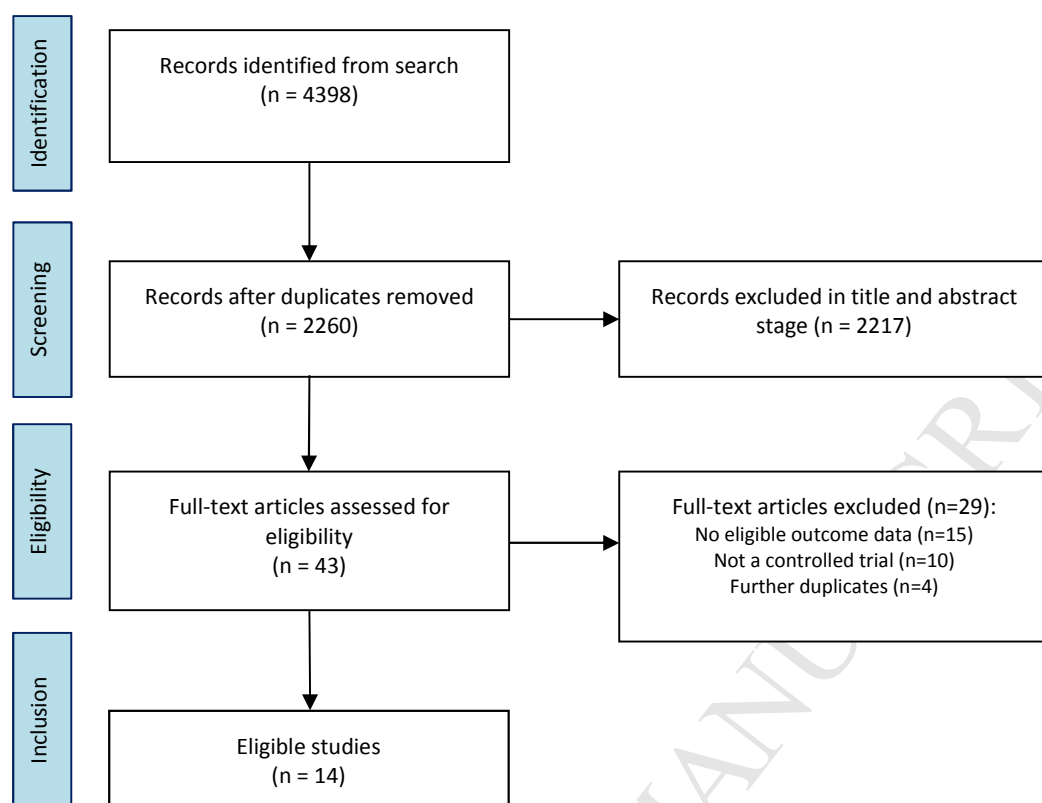
Scheewe et al (2013)	30	28.5	31.1	78	Schizophrenia	Occupational therapy	6 months stationary cycling (60 mins, 2x/wk) at increasing intensity from 45% up to 75% HR reserve.	Automated (using 'fMRIB' tool)	No effects of exercise on cerebral, cerebral grey and white matter, lateral and third ventricle volume.
Thomas et al (2016)	54	33.7	33.7	43.5	Young adults	Waitlist (inactive)	6 weeks stationary cycling (30 mins, x5/wk) at 55%-85% of maximum HR.	Automated (using 'fMRIB' and 'Freesurfer' tools)	Significant increases in anterior region of hippocampus, with no change in the thalamus from exercise.

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Notes: HCV, hippocampal volume. HR, heart rate

**Table 2.** Meta-analyses of studies reporting the effect of aerobic exercise on hippocampal volume

	Sample		Meta-analysis				Heterogeneity		
	Studies	Total n	Hedge's <i>g</i>	95% CI		P value	Q-value	P value	I <sup>2</sup>
<i>Total volume</i>	14	737	0.120	-0.02	0.26	0.082	14.1	0.371	7.45
<i>Left hippocampus</i>	9	501	<b>0.265</b>	0.090	0.441	<b>0.003</b>	5.139	0.743	0.00
<i>Right hippocampus</i>	9	501	0.164	-0.010	0.339	0.065	4.850	0.773	0.00
<i>Healthy older adults - total</i>	6	390	0.146	-0.011	0.303	0.068	4.676	0.457	0.00
<i>Healthy older adults – left</i>	5	332	<b>0.355</b>	0.137	0.572	<b>0.001</b>	2.390	0.664	0.00
<i>Healthy older adults – right</i>	5	332	<b>0.237</b>	0.021	0.453	<b>0.032</b>	2.098	0.718	0.00
<i>Psychotic disorders - total</i>	4	107	0.149	-0.31	0.60	0.530	4.67	0.197	35.8
<i>Psychotic disorders - left</i>	2	69	0.016	-0.45	0.48	0.945	0.41	0.839	0.00
<i>Psychotic disorders - right</i>	2	69	-0.036	-0.50	0.43	0.878	0.05	0.830	0.00



Study name	Outcome	Statistics for each study							
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Total
Brinke et al 2015	total	0.521	0.427	0.182	-0.316	1.358	1.220	0.223	21
Burzynska et al 2017	total	0.243	0.130	0.017	-0.012	0.498	1.869	0.062	124
Erickson et al 2011	total	0.005	0.129	0.017	-0.248	0.258	0.039	0.969	120
Jonasson et al 2016	total	0.035	0.259	0.067	-0.473	0.543	0.135	0.893	58
Krogh et al 2014	total	0.030	0.223	0.050	-0.407	0.467	0.133	0.894	79
Lin et al 2015	total	0.026	0.358	0.129	-0.676	0.729	0.073	0.942	30
Maas et al 2015	total	0.091	0.346	0.119	-0.586	0.769	0.265	0.791	32
Malchow et al 2015	total	-0.049	0.314	0.099	-0.664	0.566	-0.155	0.877	39
Morris et al 2017	total	-0.246	0.228	0.052	-0.693	0.201	-1.078	0.281	76
Niemann et al 2014	total	0.263	0.360	0.130	-0.443	0.968	0.730	0.466	30
Pajonk et al 2010	total	1.118	0.512	0.263	0.114	2.122	2.182	0.029	16
Rosano et al 2016	total	0.802	0.406	0.165	0.006	1.598	1.975	0.048	26
Scheewe et al 2013	total	-0.184	0.348	0.121	-0.866	0.499	-0.528	0.598	32
Thomas et al 2016	total	0.352	0.270	0.073	-0.178	0.881	1.301	0.193	54
		0.120	0.069	0.005	-0.015	0.255	1.738	0.082	737

-2.00

-1.00

0.00

1.00

2.00

Favours Control

Favours Exercise

Hedges's g and 95% CI

